# Assessment of Factors Affecting Hospital Readmission in Inpatients with Chronic Heart Failure

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# Abstract:

## Background

Heart Failure is a chronic cardiac condition that results in the heart being unable to pump the required amount of blood to meet the body's metabolic needs. Its severity, multimorbidity and polypharmacy are all associated with short-term hospital readmissions, although it is unknown which is the strongest factor.

## Methods

A prospective cohort study enrolled elderly Chronic Heart Failure patients from a single tertiary care hospital. Clinical, pharmacological, psychological, and demographic data were collected, while numerous assessments were tested discharge medications. Univariate and multivariate analyses were conducted to determine factors that were associated with hospital readmissions, both independently and in the presence of other factors.

## Results

Of 56 participants, 55.4% were readmitted throughout the study period and 28.6% of readmissions occurred within 30 days. 96% of patients suffered from polypharmacy, although scores for Beers Drugs criteria, Drug Burden Index and Anticholinergic Risk Scale were low. Aspects of pharmacology, such as the number of different medications prescribed and the number of high-risk drugs present, provided significant results in univariate analyses, however, no aspects of patient medication significantly influenced hospital readmission in multivariate analyses.

## Results

The population was heavily biased towards polypharmacy. Despite polypharmacy being highly prevalent, patient medications appeared to be appropriately prescribed. While some patients of patient medication may have influenced short-term hospital readmissions when analysed independently, they did not influence hospital readmission in the presence of other factors. Further research is required with more balanced study groups to accurately assess the effects of polypharmacy on Chronic Heart Failure populations' hospital readmission.

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# Assessment of Factors Affecting Hospital Readmission in Inpatients with Chronic Heart Failure

## Introduction

As Australian society continues to develop, its population will continue to age. While this increased life expectancy allows for a better quality of life for more extended periods, it also leaves elderly Australians more prone to suffering from chronic disease. One such condition elderly Australians tend to suffer from compared to their youthful counterparts includes Chronic Heart Failure (CHF), a cardiac condition that ultimately results in the heart being unable to pump the required amount of blood to meet one's metabolic needs. Self-reports from the Australian Bureau of Statistics estimate that 104,900 people aged 18 and over suffer from CHF, about two-thirds of which were adults aged 65 and over[1]. While this statistic may seem small, it is essential to note that this it may underrepresent the actual proportion of Australians suffering from CHF, as some people may be unaware of their condition or unable to diagnose it properly[2].

Australians suffering from CHF also tend to suffer from several other chronic conditions, or comorbidities, resulting in what known as multimorbidity. European surveys suggest that up to 74% of CHF patients suffer from at least one comorbidity and that up to 43% suffer from two or more comorbidities[3]. Some of these comorbidities are directly linked to CHF, while others are associated with the aging process. Chronic Renal Failure, for instance, is directly linked to CHF as it results in the kidneys oversecreting renin, a renal marker responsible initiating the Renin-Angiotensin-Aldosterone (RAAS) System which in turn elevates blood pressure and cardiac output. Abusing the RAAS System to compensate for renal insufficiency results in the heart being unable to maintain an elevated workload, and with that weakens the cardiac muscle in the heart to cause CHF. Consequently, CHF leads to reduced blood reaching the kidneys, reinitiating the RAAS system and exacerbating both conditions in what is known as Cardiorenal Syndrome[4]. Comorbidities such as Chronic Obstructive Pulmonary Disorder (COPD), on the other hand, are often the result of lifestyle habits such as smoking but still contribute towards the development and exacerbation of CHF. As lung tissue degrades in COPD and oxygen absorption reduces, the respiratory system forces arterial pressure in the pulmonary arteries to

rise, resulting in pulmonary hypertension. This increase in pressure places excessive strain on the right ventricle on the heart as it pumps blood to the lungs, resulting in the cardiac muscle weakening and causing right-sided heart failure. Right-sided heart failure increases the workload of the left ventricle, ultimately resulting in left-sided heart failure[5].

Elderly CHF patients that also suffer from multimorbidity also tend to suffer from polypharmacy. While the scientific community is yet to decide on the concrete definition of polypharmacy, scientific literature often describes it as the concurrent use of five or more prescription medications[6, 7]. American studies show that 52% of CHF patients over the age of 75 suffer from polypharmacy, and French studies suggest that the number of different prescription medications given to CHF patients increases from 4.8 to 6.4 after being hospital discharge[8, 9, 10]. It is important to note that some of these medications may bear anticholinergic or sedative risks. While tolerable in younger populations, elderly patients are more susceptible to the adverse side effects associated with anticholinergic and sedative medications. Anticholinergics function by blocking muscarinic receptors on nerve endings, acting as competitive inhibitors to acetylcholine (ACh), while sedatives work by increasing Gamma-Aminobutyric Acid (GABA) release in the Central Nervous System[11]. Despite having their benefits in conditions such as COPD or anxiety, anticholinergic and sedative medications can negatively impact elderly patients if misused. These can range from mild inconveniences such as dry mouth or dizziness to severe conditions such as dementia or hypothermia, decreasing quality of life[12]. Estimates suggest that up to 25% of CHF patients suffer from adverse reactions to anticholinergic or sedative at any capacity; an unnecessary burden for already ill people[13].

CHF patients are readmitted into hospital at excessively high rates. Australian studies show that between 25 – 30 % of all CHF patients are either readmitted into hospital or die within 30 days of initial hospital discharge, compared to the national average of approximately 15% for all hospital readmissions[14, 15]. These rates are exceptionally high when comparing CHF as a condition to other chronic diseases such as cardiovascular disease (14.7) and stroke (6.4%) and cardiovascular disease (1.7%)[16, 17]. Abnormally high readmissions into hospital and other adverse short-term events place

financial and logistical strain on the healthcare system, costing it approximately $2B per year within the next ten years[18].

It is known that CHF is associated with exceptionally high short-term readmission rates and that multimorbidity and polypharmacy are also associated with high readmission risk and thus influence short-term hospital readmissions[19]. It is unknown, however, whether these factors independently influence short-term readmissions or do so as the result of the other factor. The effects of mental health such as depression and anxiety are also unknown and have the potential to impact a CHF patient's ability to adhere to treatment regimens, and with that, increase the likelihood of hospital readmission if unable to do so. As a result, this research study will examine the factors that most strongly influence short-term hospital readmissions and other adverse outcomes in CHF patients.

Polypharmacy is a strong indicator of short-term hospital readmission for other chronic conditions. Picker et al.'s 2015 study in assessing polypharmacy as an indicator of short-term hospital readmission in all inpatients found a significant and independent association between six or more different prescription medication and short-term hospital readmission (Odds ratio = 1.3, 95% Confidence Interval, 1.2 – 1.4, p = 0.003) and a significant association between an increase in prescription medication upon discharge and short-term hospital readmission[20]. Thus, it is hypothesised that polypharmacy is the strongest factor regarding short-term hospital readmissions for CHF patients in comparison to other variables such as physical and social factors. This study will attempt to holistically review pharmacological, social, psychological, and physical factors in inpatients suffering from CHF in order to:

- Assess readmission within 30 days.
- Assess potentially inappropriate medication within the study population.
- To identify possible variables that are constant in individuals with poor short-term outcomes in an attempt to target patients with these variables for future interventions.

# Methods

## Study Population

The study was conducted at the Royal Adelaide Hospital (RAH), a tertiary referral metropolitan hospital with approximately 700 beds. The research team prospectively enrolled participants throughout March – July 2020, as well as data gathered from CHF patients in 2019. Their population of interest comprised of inpatients aged 50 or older suffering from CHF, which was defined as either their reason of admission into the RAH, suffered from CHF at the time of admission or use prescription medications exclusive to CHF patients, such as Bisoprolol. Other inclusion criteria included the ability to provide either written or verbal informed consent, have sufficient English language skills to answer study questions and comply with study procedures. Patients were excluded if they were discharged to high-level residential aged care, had palliative intent or cognitive impairment which would interfere with providing informed consent and study assessments, or those whose clinical team felt would otherwise be inappropriate for the study. The research team used Allscripts Sunrise Electronic Health Record (Allscripts, Chicago, IL) to filter inpatients to only display those who explicitly suffer from CHF, or use medications prescribed exclusively for CHF patients (e.g., bisoprolol). Medical records were checked for age, to confirm disease diagnosis and to review residential status. Clinical staff on hospital wards were also approached to confirm patient eligibility. Once deemed as appropriate for the study, the research team then directly approached patients, informed them about the study and invited them to participate. Figure 1 provides a flowchart of the number of participants involved at each stage of the study.

## Data Collection

Once the patient provided informed consent, the research team collected data through the following assessments. Participants were asked about the number of general practitioners, specialists and pharmacies they had seen in the last twelve months, whether they had received Chronic Disease Care Plans or Home Medicines Review and asked about their living situations. Hilmer et al.'s modified Reported Edmonton Frail Scale was used to assess frailty alongside the Clinical Frailty Scale and Barthel's Index to gain an understanding of the participants' general health[21]. Emotional wellbeing was measured through the 21-item Depression Anxiety and Stress Scales (DASS-21), while the Multidimensional Health Locus of control was used to measure the factors that participants believed

controlled their health[22, 23]. Comorbidities and medications were collected from participant's case notes or their Electronic Medical Record. Blood test results, final discharge dates and subsequent readmissions were gathered from Open Architecture Clinical Information System (OACIS) v 7.1.0.106 (OACIS, Telus Health, Longueil, Canada). In the event that participants were discharged before baseline data collection was completed, any remaining assessments were either sent in the mail or completed over the phone. It is also important to note that some participants were unable to complete the cognitive component of the Reported Edmonton Frailty test due to several reasons, and thus were not asked to undertake it. When analysing the data, participants who were unable to complete the cognition component of the test were excluded when analysing Reported Edmonton Frailty Test data.

## Assessment of Medications

The research team counted the total number of regular discharge medicines and administrations per day from either the patient's discharge summary or case notes. It is important to note, however, that medications that were taken as required or prescribed for short periods were excluded from their count. Polypharmacy was defined as the use of five or more regular medications, while hyperpolypharmacy was defined as the use of ten or more regular medications as agreed upon in the general scientific community[24, 25]. The 2015 and 2019 American Geriatrics Society Beers Criteria for Potentially Inappropriate Medication Use in Older Adults were used to assess the appropriateness of patient medications[26, 27]. These two criteria were used alongside the Drug Burden Index and the Anticholinergic Risk Scale to assess for anticholinergic and sedative burden[28, 29, 30, 31]. The research team used these different criteria to analyse participant medications for further analysis comprehensively.

## Measurement of Outcomes

Time to readmission was the primary outcome measured. The research team used OACIS to determine when participants were readmitted into hospital, including all unplanned readmissions. Emergency department (ED) admissions were also included in this count and were not recounted if a patient was transferred into a ward and then reappeared in ED. Secondary outcomes included readmission within 30 days. Date of death, when applicable, was sourced from OACIS. Patients who were lost to follow

up had their censor dates recorded as their last form of contact, including follow up assessments or outpatient appointments at the Royal Adelaide Hospital.

### Statistical Analysis

The research team used SPSS version 26 (IBM Corp, Armonk NY, USA) to analyse its data. Firstly, the non-parametric one-sample Kolmogorov-Smirnov test was used to determine if scale data were normally distributed or not. At this point, scale data not normally distributed were analysed by the independent samples T-test while normally distributed scale data was analysed using non-parametric independent samples Mann-Whitney U test. Kaplan-Meier analyses were used to conduct univariate survival analyses of time to readmission. Significant or near significant results from the Kaplan-Meier analyses (i.e. $P < 0.2$) were used in a Cox Regression multivariate analysis for time to readmission. Variables possessing the great p-value were removed from the analysis until a final model, with all variables producing p values of $< 0.05$, was produced. Polypharmacy and other aspects of participant medications were then integrated into this model to determine how powerful an influence they are on participant readmissions in comparison to the already-present variables. When using scale data such as BMI or the number of different medications prescribed to analyse time to readmission in univariate and multivariate analyses, it was categorised to analyse it in a simple manner while also comparing distinct groups of participants. For instance, BMI was categorised into differing weight ranges such as underweight, healthy weight, overweight and obese, while the number of different prescription medications was categorised to compare individuals with more than fifteen medications to those with less than fifteen medications.

## Ethical Considerations

This study was approved by the Central Adelaide Local Health Network Human Research Ethics Committee (reference number: R20190301). All participants gave written or verbal informed consent and were given a copy of their consent form.

Consort Diagram

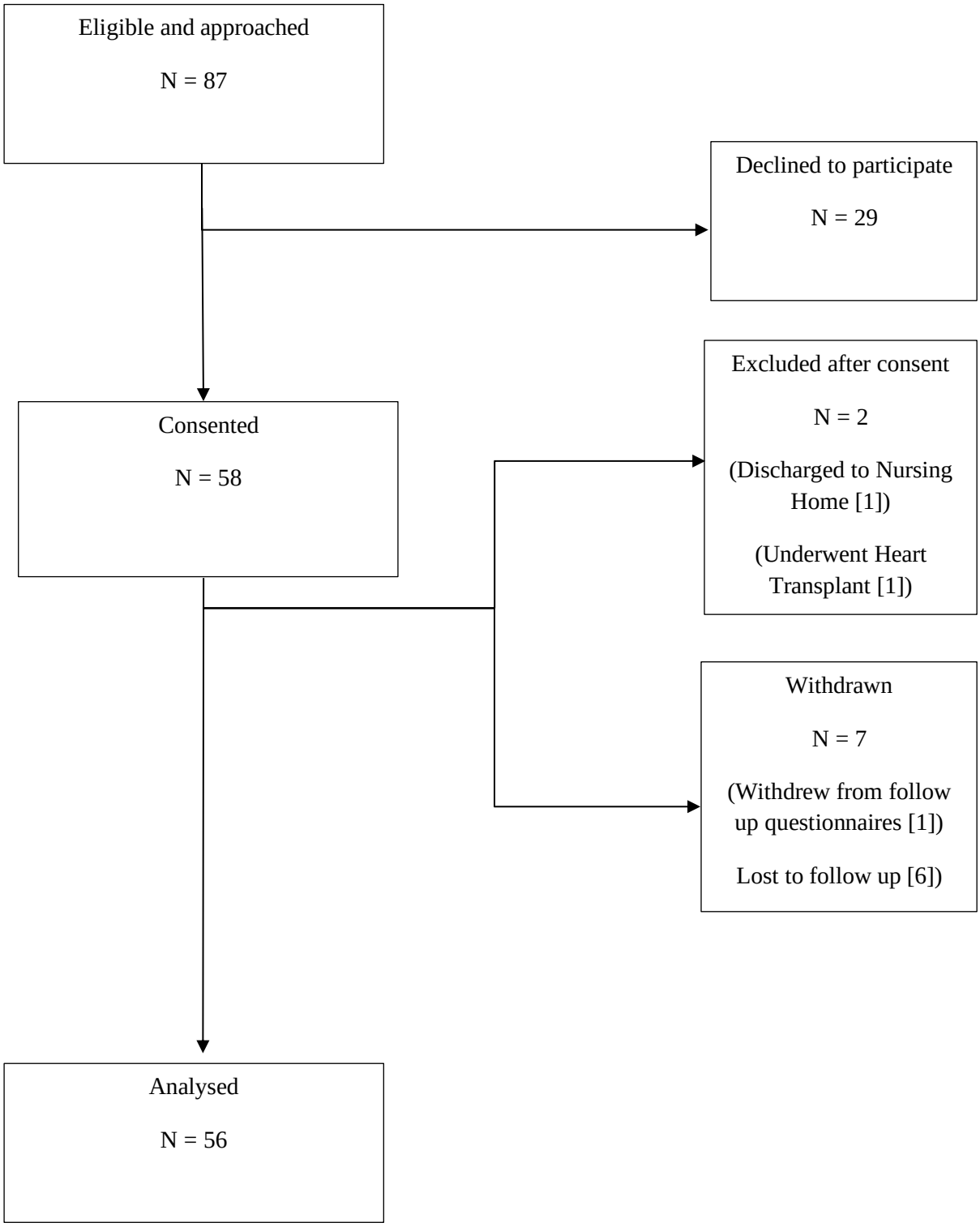


Figure 1: A CONSORT diagram showing the recruitment process of the study

# Results

Fifty-eight participants were enrolled in the study, with 56 having results analysed following the exclusion of two participants. 55.4% of participants were readmitted throughout the study, and 28.4% of all participants were readmitted into hospital within 30 days of initial discharge. The participants were predominantly male, and the mean age of the cohort was 69.7 years (± 9.2, 51 – 91). Further demographic and clinical information is available in Table 1.

Table 1: Demographic and clinical traits of the study cohort.

| | **Statistics (N=56)** |
|---|---|
| **Age at Consent (Years)** | 69.7 ± 9.2, 51– 91 |
| **Weight at Consent (Kg)** | 92.8 ± 23.9, 45 – 162 |
| **Height at Consent (Cm)** | 170.0 ± 9.1, 152 - 186 |
| **Body Mass Index (BMI)** | 32.16 ± 8.45, 15.57 – 53.83 |
| **Gender (Male)** | 36 (64.3%) |
| **Country of Birth (Born In Australia)** | 39 (69.6%) |
| **Living Situation (With Someone Else)** | 26 (46.4%) |
| **Rural Residency** | 14 (25%) |
| | |
| **Smoking Status: (N = 53)** | |
| **Current Smoker** | 8 (15.1%) |
| **Ex-Smoker** | 28 (52.8%) |
| **Never Smoked** | 17 (32.1%) |
| | |
| **Readmitted After Discharge** | 31 (55.4%) |
| **Readmission Within 30 Days** | 16 (28.6%) |
| **Total Comorbidities** | 7, 5 – 9 |
| **Diabetes** | 46 (82.1%) |
| **Hypertension** | 39 (69.6%) |
| **Ischaemic Heart Disease** | 34 (60.7%) |
| **Hypercholesterolemia** | 32 (57.1%) |
| **Atrial Fibrillation** | 27 (48.2%) |
| **Chronic Renal Failure** | 18 (32.1%) |
| **Depression** | 14 (25.0%) |
| **Chronic Obstructive Pulmonary Disease** | 13 (23.2%) |
| **Anaemia** | 13 (32.1%) |
| | |
| **Hba1c (Mol/L)** | 7.9 ± 1.8, 5 – 11.9 |
| **Creatinine (Mol/L)** | 1.6 ± 0.7, 0.2 – 3.3 |
| **Haemoglobin (Mg/Dl)** | 107.5, 99 – 137.8 |
| **Low-Density-Lipoprotein (Mol/L)** | 1.6 ± 0.7, 0.2 – 3.3 |
| **High-Density-Lipoprotein (Mol/L)** | 0.9, 0.7 – 1.3 |
| **Estimated Glomerular Filtration Rate (mL)** | 47.5, 32.3 – 69.5 |
| **Creatinine Clearance (mL)** | 72.4 ± 45.5, 17.1 – 213.2 |

Table 2 summarises patient medications. Patients, on average, were prescribed 11.1 different medications upon hospital discharge. 54 (96.4%) patients suffered from polypharmacy, while 35 (62.5%) of patients suffer from hyperpolypharmacy, which is generally described as the use of 10 or more prescription medications. The 2015 and 2019 Beers Drugs Criteria scores were both low (median = 0.0, IQR = 0.0 – 1.0), as were Drug Burden Index scores (median 0.4, IQR 0.0 – 0.7). The cohort also displayed a median score of 0 on the Anticholinergic Risk Scale (IQR 0 – 0). Despite these numbers, the median number of Drug-Drug Interactions was 1 (IQR 0 – 2).

Table 2: A summary of patient medications.

| | **STATISTICS (N=56)** |
|---|---|
| **Number of Different Medications Upon Discharge** | 11.1 ± 4.2, 3.0 – 22.0 |
| **Number of Administrations Per Day** | 14.6 ± 6.3, 4.0 – 31.0 |
| **Polypharmacy** | 54 (96.4%) |
| **Hyperpolypharmacy** | 35 (62.5%) |
| **Acetylcholine Risk Scale Score** | 0.00, 0.00 – 0.00 |
| **Drug Burden Index Score** | 0.42, 0.00 – 0.67 |
| **Number of Beers 2019 Drugs** | 0.0, 0.0 – 1.0 |
| **Number of Beers 2015 Drugs** | 0.0, 0.0 – 1.0 |
| **Drug Burden Index Score** | 0.4, 0.0 – 0.7 |
| **Total Number of High-Risk Drugs** | 1.0, 0.0 – 2.0 |
| **Duplicate Drugs** | 0.0, 0.0 – 0.0 |
| **Sedative Drugs** | 0.0, 0.0 – 0.0 |
| **Anticholinergic Drugs** | 0.0, 0.0 – 0.0 |
| **Drug-Drug Interactions** | 1.0, 0.0 – 2.0 |

The results from the frailty tests conducted and psychological tests such as the DASS-21, are summarised in table 3. 51 participants completed the cognition component of the Edmonton Frail Scale; thus, only the total score with 51 participants is recorded. Findings from the Edmonton Frail Scale are categorised according to the classification from Hilmer et al.'s version of the frailty test. Barthel's Index scores were categorised in increments from ten, starting from seventy. Clinical Frailty scores were classified in increments of one, starting from three, while Barthel's Index scores were classified in increments of ten, starting from seventy. DASS-21 and Locus of Control scores were not categorised in any particular manner.

Table 3: A summary of test results regarding frailty, mental wellbeing and personal beliefs regarding health.

| | **STATISTICS (N=56)** |
|---|---|
| **Edmonton Frailty Test:** | |
| • **Not Frail (0 – 5)** | 26 (46.4%) |
| • **Vulnerable (6 – 7)** | 14 (25.0%) |
| • **Mildly Frail (8 – 9)** | 10 (17.8%) |
| • **Moderately Frail (10 – 11)** | 3 (5.4%) |
| • **Severely Frail (12+)** | 3 (5.4%) |
| **Edmonton Frailty Test (Without Cognition)** | |
| • **Not Frail (0 – 5)** | 21 (37.5%) |
| • **Vulnerable (6 – 7)** | 8 (14.3%) |
| • **Mildly Frail (8 – 9)** | 17 (30.4%) |
| • **Moderately Frail (10 – 11)** | 5 (8.9%) |
| • **Severely Frail (12+)** | 5 (8.9%) |
| **Barthel Index (N=55):** | |
| • **<70** | 6 (10.91%) |
| • **70 – 80** | 5 (9.09%) |
| • **80 – 90** | 12 (21.82%) |
| • **>90** | 32 (58.18%) |
| **Clinical Frailty Score (N=55):** | |
| • **=<3 (Not Frail)** | 14 (25.50%) |
| • **4 (Mildly Frail)** | 17 (30.90%) |
| • **5 (Moderately Frail)** | 16 (29.10%) |
| • **=>6 (Severely Frail** | 8 (14.50%) |
| **Dass-21 Depression Subscale** | 4.00, 2.00 – 10.00 |
| **Dass-21 Anxiety Subscale** | 5.00, 3.00 – 11.00 |
| **Dass-21 Stress Subscale** | 6.00, 2.00 – 9.50 |
| **Locus of Control (Internal)** | 24.00, 20.00 – 26.25 |
| **Locus of Control (Chance)** | 17.26 ± 7.57, 6.00 – 32.00 |
| **Locus of Control (Powerful Others)** | 23.12 ± 6.60, 7.00 – 36.00 |

Kaplan-Meier survival functions were used to provide the probability of an object of interest; in this instance, participants enrolled in the study encountering an event within a certain time frame. In this study, the event was hospital readmission at any time during the study period. It is important to note that Kaplan-Meier survival functions are a univariate analysis, meaning that they only assess one variable at any given instance.

The Kaplan-Meier survival functions generated showed that numerous variables were significantly associated with hospital readmissions when analysed independently. These variables include the total score of the Reported Edmonton Frailty Test, reported number of the falls in the last 12 months, Clinical Frailty scores, BMI, and the presence of hypertension. They also provided near-significant results ($p > 0.2$) for variables regarding hospital readmissions. Aspects of patient medications such as the number of different medications taken and Drug Burden Index scores were near significant, as well as comorbidities such as asthma and osteoarthritis. Despite some data showing significant or near-significant results, such as Acetylcholine Risk Scale score and Left Ventricular Ejection Fraction, there was no identifiable relationship between the variable and hospital readmissions. Thus, they were deemed biologically implausible and excluded from the Cox-Regression multivariate analysis. A comprehensive table detailing the relationships between hospital readmission and the data gathered, as well as other issues found in the data, can be viewed in the appendix.

Table 4 shows the final model generated by the Cox-Regression analysis. Factors pertaining to polypharmacy and other aspects of patient medications were then assessed against the shown variables to determine if polypharmacy significantly contributed to hospital readmission in the presence of other variables. No aspects of patient medication, including polypharmacy, significantly contributed towards hospital readmissions in the presence of other variables.

Table 4: Results from the multivariate Cox-Regression analysis of time to readmission.

| | Regression Coefficient (B) | Standard Error | Sig (p-value) | Hazard Ratio Exp(B) | 95.0% Confidence Interval | |
|---|---|---|---|---|---|---|
| | | | | | Lower | Upper |
| **Falls 12 months** | 1.6 | 0.55 | 0.003 | 5.1 | 1.8 | 15.0 |
| **Hypertension** | 2.2 | 0.89 | 0.015 | 8.7 | 1.5 | 49.4 |
| **Asthma** | 2.8 | 0.88 | 0.002 | 16.0 | 2.8 | 90.0 |
| **Osteoarthritis** | 2.6 | 0.94 | 0.006 | 13.1 | 2.1 | 83.0 |
| **Hypercholesterolemia** | 1.4 | 0.68 | 0.041 | 4.0 | 1.1 | 15.2 |
| **Reported Edmonton Frailty Test (Total)** | 0.29 | 0.089 | 0.001 | 1.3 | 1.1 | 1.6 |
| **BMI** | -0.069 | 0.029 | 0.017 | 0.93 | 0.88 | 0.98 |

# Discussion

Over half the study cohort was readmitted into hospital throughout the study period, with 30% of all participants readmitted within 30 days. The study group was predominantly male, with the average age of participants being close to seventy years old. The cohort was also generally overweight, if not obese, and typically suffered between five to nine comorbidities. The majority of the cohort suffered from diabetes (82.1%), hypertension (69.6%), ischaemic heart disease (60.7%), hypercholesterolemia (57.1%), and atrial fibrillation (48.2%). However, conditions such as anaemia and COPD were not as frequently reported (32.1% and 23.3% respectively) relative to the comorbidities mentioned above. These findings are somewhat consistent with what is known in the literature. While most CHF patients typically suffer from atrial fibrillation, ischaemic heart disease and hypertension, non-cardiovascular diseases such as chronic renal disease were also apparent in other study cohorts[32, 33]. Diabetes was heavily over-represented, as other heart failure study cohorts typically have 25% of participants have diabetes[34]. The discrepancies in these statistics may be due to the small sample size of this study's cohort, as only 56 sets of data were gathered by the end of the study period in comparison to other studies that typically comprise of thousands of participants.

Over 96% of the participants suffered from polypharmacy. Other studies typically show that at least 50% of CHF patients suffer from polypharmacy in some capacity, with even less suffering from hyperpolypharmacy. Australian studies focusing on polypharmacy in all patients report that 36.1% and 43.3% of Australians aged ≥70 and ≥50 respectively suffer from polypharmacy[35]. It is important to note, however, that there is limited information regarding the presence of polypharmacy in Australian CHF inpatients. By averaging 11.1 different medications, the study cohort also uses more medication than cohorts in other CHF studies, which have been found to use up to 6.8 different medications[36]. The number of medications is typically an indicator of health outcomes as using a higher number of different medications

increases the likelihood of drug-drug interactions and inappropriately prescribed medications being used. In saying that, this study cohort displayed low scores for both the 2015 and 2019 Beers Criteria, Drug Burden Index and Anticholinergic Risk Scales, implying that their medications were appropriately prescribed. These findings may be due to heart failure patients suffering from multiple comorbidities; thus, medical professions may prepare more carefully thought out treatment regimens to ensure that medications intended for heart failure do not negatively affect the outcome of a given comorbidity.

The univariate analyses suggest that the number of different GP practices and pharmacies participants visit, Reported Edmonton Frailty Test and Clinical Frailty scores, the number of falls in the last twelve months and BMI all significantly contribute towards hospital readmission when analysed independently. Anticholinergic Risk Score, Beers Drug Scores and Conflicting Treatment scores also significantly contributed towards hospital readmission when analysed independently, despite generally being low for the cohort. It is important to note, however, that the Anticholinergic Risk Score, Beers Drug Scores, Conflicting Treatment score and the number of different GP practices visited were all not biologically plausible. They did not correspond to trends set in the scientific literature and therefore, were not considered appropriate factors to influence short-term hospital readmissions independently[36,37]. BMI and Reported Edmonton Frailty Test Scores both provided significant values and were biologically plausible, thus in this study cohort can be considered factors that influenced hospital readmissions in a vacuum.

After removing all statistically insignificant variables, the multivariate analysis showed that the number of falls in the last twelve months, hypertension, asthma, osteoarthritis, hypercholesterolemia, Reported Edmonton Frailty Score and BMI all significantly contributed towards hospital readmission in the presence of other factors, with other studies reporting that the odds of readmission increase by 1.12 percent per point scored in the Reported Edmonton

Frailty Test. These findings are mostly consistent with that is known in the literature, for instance, hypertension and hypercholesterolemia are risk factors for CHF[32] while reporting a high number of falls in the last twelve months or high scores on the Reported Edmonton Frailty test indicate that increased frailty results in increased hospital readmissions, a finding present in all ill people[38]. It was noted that the hazard ratio for BMI was < 1, indicating an inverse relationship between BMI and hospital readmission. While this relationship initially seems biologically implausible, scientific literature suggests that it may be due to the Obesity Paradox, which suggests that increased BMI are independently associated with a lower risk of death and death due to worsening Heart Failure[39]. In the multivariate model, no aspects of polypharmacy or patient medications showed significant or near-significant results, despite univariate analyses suggesting otherwise.

The lack of significant findings for polypharmacy and patient medications in the multivariate analysis may be due to the study cohort's small sample size, the demographics of the study cohort and the screening requirements to partake in the study. The study cohort only comprised of 56 participants by the end of the study period, 54 of which suffered from polypharmacy. This means that the non-polypharmacy group only consists of two participants, which is an insufficient number when being examined as the strongest indicator of hospital readmission. While it can be argued that small sample sizes may result in significant findings occurring through sheer coincidence, the final Cox-Regression model shows a number of factors that both biologically plausible and shown in other studies to significantly contribute towards hospital readmissions[3, 10, 19, 32, 33]. As a result, the number of participants enrolled in the study may not be accountable for the lack of significant findings regarding polypharmacy. It is also essential to consider that the majority of participants were sick, older adults who also tend to see medical professionals frequently[40], and with that do not adequately reflect the situation of younger patients or those unable to contact healthcare services consistently.

As mentioned earlier, the number of different medications the study cohort had greatly exceeded those in similar studies[7, 8, 19]. While it is scientifically plausible to assume that the probability of hospital readmission is directly proportional to the number of different medications taken, as seen in the univariate analyses which display an association between these two variables, it is essential to consider how properly, or poorly, these drugs are prescribed and interact with each other. Patient medications, despite being high in quantity, treatment regimens were appropriately prescribed. Both 2019 and 2015 Beers Drugs Criteria scores had median scores of 0.0 (IQR 0.0 – 1.0), Drug-Drug Interaction score had a median score of 1.0 (IQR 0.0 – 2.0), and few high-risk drugs were prescribed to participants (median score of 1.0, IQR 0.0 – 2.0). Participants were at low risk of any anticholinergic risk (median score 0.0, IQR 0.0 – 0.0) and generally had low scores on the Drug Burden Index (median score 0.42, 0.00 – 0.67). As medications were appropriate prescribed, it also meant unlike the presence of pharmacology, the number of participants scoring on these drug assessment criteria are generally low. This was not applicable to some variables, such as the Drug Burden Index scores and total high-risk drugs, which had rather even groups and thus produced near-significant results ($p = 0.08$ and 0.06 respectively). It is also important to note that despite some aspects of patient medication providing near significant results in the Kaplan-Meier analyses, the probability of hospital readmission was not directly nor inversely proportional to trends in the data. Acetylcholine Risk Scale scores, for instance, produced a p-value of 0.04, but when categorising the data to compare two distinct groups, the findings did not stay significant, in this instance the p-value for Acetylcholine Risk Scale score equalling 0.58 when comparing scores of zero to scores greater than zero.

The prospective design of the study is one of the strengths it possesses; however, small sample sizes and only one location to gather data impinge the ability to generalise findings. A more extensive study would allow for a greater sample size to be examined for a more extended period not only to gather more data regarding short-term hospital readmissions but potentially delve into the impacts each variable has on long-term hospital readmissions. Despite the length of time allocated for the study period, it was able to create a complex data set of a complicated group of inpatients which can thus be further analysed in future studies. With this in mind, it is essential to maintain compliance for assessments to allow for as much data to be collected as possible.

It is important to note that the study design also had a number of flaws. One such shortcoming was failing to recruit enough participants to meaningfully contribute to the non-polypharmacy group. Pre-screening participants based on the number of different medicines they are prescribed may circumvent this issue. Thus, a study cohort that distributes polypharmacy and non-polypharmacy more evenly can be created to allow for sufficient data to be collated for both study groups. The vast majority of participants also lived in urban or suburban areas, and with that unable to properly reflect outcomes in rural or remote CHF patients. Readmission data collected from OACIS were only able to include data for public hospitals; thus, readmissions may have been missed if participants were readmitted in private hospitals. Older patients who are severely ill would tend to use more medications, which may explain the difference in numbers between the polypharmacy and non-polypharmacy groups.

# Conclusion

Polypharmacy was observed at a much higher rate in the study group than in Australia and other developed nations; however, medications were mostly prescribed appropriately. Keeping this in mind, polypharmacy and other patient factors displayed some association with hospital readmissions when analysed individually, however, did not significantly contribute towards hospital readmission in complex situations such as those in CHF patients. The research provides an insight into the factors that contributed towards hospital readmissions in the study group, such as aspects of frailty and comorbidities associated with CHF. Improving the study design by allowing for larger sample sizes and more evenly distributed cohorts between polypharmacy and non-polypharmacy groups may produce more meaningful results regarding polypharmacy and patient medications.

Word Count: 4,395 words

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# Appendix

| Factor | Categorisation (Scale Data Only) | P Value | Comments |
|---|---|---|---|
| **Number Of Different Medications** | 3 categories:<br>- < 10 medications<br>- 10 – 14 medications<br>- > 15 medications | 0.16 | Using less than ten different medications led to a smaller probability of hospital readmission. In most instances, using fifteen or more different medications resulted in a higher probability of hospital readmission. The data was recategorized into two groups: participants that use less than fifteen different medications and those that use more than fifteen different medications. |
| **Number Of Different Medications** | 2 categories:<br>- < 15 medications<br>- >= 15 medications | 0.15 | Using less than fifteen different medications led to a smaller probability of hospital readmission. |
| **Acetylcholine Risk Scale Score** | Unchanged | 0.04 | The probability of hospital readmission in participants were neither directly nor inversely proportional to Acetylcholine Risk Scale scores. Thus, the data was recategorized into two groups: scores equal to zero and scores greater than zero. |
| **Acetylcholine Risk Scale Score** | 2 categories:<br>- Scores of 0<br>- Scores greater than 0 | 0.58 | |
| **Drug Burden Index Score** | 2 categories:<br>- Scores of 0<br>- Scores greater than 0 | 0.08 | A Drug Burden Index Score of zero resulted in a lower likelihood of hospital readmission in comparison to Drug Burden Index scores greater than zero. |
| **Reported Edmonton Frailty Scale (Total)** | unchanged | 0.06 | The probability of hospital readmission in participants were neither directly nor inversely proportional to the total Reported Edmonton Frailty score. Thus, the data was reassessed using the categories derived from Hilmer et al's Reported Edmonton Frailty |

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| **Reported Edmonton Frailty Scale (Total)** | 5 categories:<br>- Not frail (0 – 5)<br>- Vulnerable (6 – 7)<br>- Mildly frail (8 – 9)<br>- Moderately frail (10 – 11)<br>- Severely frail (12+) | 0.019 | Participants that were recorded as 'Not frail' had the lowest probability of hospital readmission. The probability of hospital readmission was directly proportional to the frailty of the participant (i.e. severely frail participants had higher probability of hospital readmission than mildly frail participants). |
| **Reported Edmonton Frailty Scale (Total)** | 3 categories:<br>- Not frail (0 – 5)<br>- Vulnerable (6 – 7)<br>- Any frailty (8+) | 0.006 | Participants that were recorded as 'Not frail' had the lowest probability of hospital readmission. Those that were reported to have 'any frailty' had the highest probability of hospital readmission. |
| **Falls (Last 12 Months)** | 2 categories:<br>- No falls<br>- Any falls | 0.033 | Participants that were recorded as not having any falls in the last 12 months had lower probability of hospital readmission in comparison to those recorded as having any falls in the last 12 months. |
| **Body Mass Index** | categorised as usual according to BMI, i.e.<br>- Underweight: BMI <18.5<br>- Healthy Weight: BMI between 18.5 and 24.9<br>- Overweight: BMI between 24.9 and 29.9<br>- Obese: BMI between 30 and 34.9<br>- Morbidly Obese: BMI > 35 | 0.017 | Participants that were recorded as obese or morbidly obese had the lowest probability of hospital readmission. Patients that were considered underweight or overweight had the highest probability of hospital readmission. The data was reassessed using the following categories: Underweight (<18.5) and not underweight (>=18.5). |
| **Body Mass Index** | 2 categories:<br>- Underweight (<18.5)<br>- Not underweight (>=18.5) | 0.002 | Participants recorded as being underweight had a higher probability of hospital readmission in comparison to those not recorded as being underweight. |

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| **Clinical Frailty** | 2 categories:<br>- Not frail (i.e. 1 – 4)<br>- Frail (i.e. 5+) | 0.024 | Participants recorded as being frail had higher probability of hospital readmission than those recorded as not frail. |
| **Left Ventricular Ejection Fraction** | categorised according to dysfunction:<br>- Severe (<30%)<br>- Moderate (30 – 39%)<br>- Mild (40 – 49%)<br>- "Normal" (>50%) | 0.085 | The probability of hospital readmission in participants were neither directly nor inversely proportional to left ventricular ejection fraction percentages. |
| **Hypertension** | | 0.009 | Participants suffering from hypertension had higher probability of hospital readmission than those that do not suffer from hypertension. |
| **Asthma** | | 0.091 | Participants suffering from asthma had a higher probability of hospital readmission than those not suffering from asthma. |
| **Osteoarthritis** | | 0.094 | Participants suffering from osteoarthritis had a higher probability of hospital readmission than those not suffering from osteoarthritis. |
| **Hypercholesterolemia** | | 0.13 | Participants suffering from hypercholesterolemia had a higher probability of hospital readmission than those not suffering from current solid tumours. |
| **Total Treatment Conflict** | unchanged | 0.001 | The probability of hospital readmission was neither directly nor inversely proportional to total treatment conflicts. Thus, the data was reassessed using two categories: no conflicts and any conflicts. |
| **Total Treatment Conflict** | 2 categories:<br>- 0<br>- >0 | 0.10 | Participants with any conflicting treatments had higher probability of hospital readmission than those with zero conflicting treatments. |
| **Total High Risk** | unchanged | 0.009 | The probability of hospital readmission was neither directly nor inversely proportional to the total number of high-risk medications. Thus, data was reassessed using two categories: zero high-risk medications and more than zero high-risk medications |
| **Total High Risk** | 2 categories:<br>- 0<br>- >0 | 0.061 | Participants reported as using any high-risk medication had a higher probability of hospital readmission than those not reported as using any high-risk medications. |
| **Duplicate Drugs** | unchanged | N/A | No participants were recorded as having any duplicate drug; thus, the data could not be assessed. |

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| **Total (Duplicate, Anticholinergic And Sedative Drugs)** | unchanged | 0.092 | The probability of hospital readmission was neither directly nor inversely proportional to the total number of duplicate, sedative and anticholinergic drugs. Thus, the data was reassessed using two categories: zero of the aforementioned drugs and more than zero drugs. |
| **Total (Duplicate, Anticholinergic And Sedative Drugs)** | 2 categories:<br>- 0<br>- >0 | 0.18 | Participants recorded as using any duplicate, sedative or anticholinergic drug had a higher probability of hospital readmission than those not using these drugs. |
| **2019 Beers Drugs** | unchanged | 0.005 | The probability of hospital readmission was neither directly nor inversely proportional to the 2019 Beers Drugs score. Thus, the data was reassessed using two categories: a score of zero and a score greater than zero. |
| **2019 Beers Drugs** | 2 categories:<br>- 0<br>- >0 | 0.55 | |
| **2015 Beers Drugs** | unchanged | 0.004 | The probability of hospital readmission was neither directly nor inversely proportional to the 2015 Beers Drugs score. Thus, the data was reassessed using two categories: a score of zero and a score greater than zero. |
| **2015 Beers Drugs** | 2 categories:<br>- 0<br>- >0 | 0.57 | |